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1287389

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February 18, 2005

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APPLICATION NUMBER: ***60/545,195***
FILING DATE: ***February 17, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US05/03060***

UNITED STATES PATENT AND TRADEMARK OFFICE
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Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
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15750 U.S.PTO
021704

Attorney's Docket No. JJA-0303 *"PATENT"*

Family Number P2004J006

322856 U.S.PTO
60/545195
021704

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Michael Siskin et al

For: SYNTHESIS OF SEVERELY STERICALLY HINDERED SECONDARY AMINOETHER ALCOHOLS FROM A KETENE AND/OR CARBOXYLIC ACID HALIDE AND/OR CARBOXYLIC ACID ANHYDRIDE

Commissioner for Patents
Mail Stop: Provisional Patent Application
P.O. Box 1450
Alexandria, Virginia 22313-1450

COVER SHEET FOR FILING PROVISIONAL APPLICATION (37 C.F.R. § 1.53(c))

CERTIFICATION UNDER 37 C.F.R. 1.10 *
(Express Mail label number is mandatory) ***(Express Mail certification is optional)***

[X] "Express Mail" mailing label number E U 8 6 3 1 0 0 7 8 9 U S . Date of Deposit February 17, 2004 .

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KATHLEEN A. KUNA	Kathleen A. Kuna
(TYPE OR PRINT NAME OF PERSON MAILING PAPER)	(SIGNATURE OF PERSON MAILING PAPER)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53(c):

1. The following comprises the information required by 37 C.F.R. § 1.51(c)(1):

2. The name(s) of the inventor(s) is/are:

	GIVEN NAME	MIDDLE INITIAL OR NAME	FAMILY (OR LAST) NAME
1.	Michael	--	SISKIN
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3.	Kostyantyn	Mykolayevich	KIRICHENKO
4.	Adeana	Richelle	BISHOP
5.	Christine	Nicole	ELIA

27810
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3. Residence address(es) of the inventor(s), as numbered above:

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   4. 2563 Costa Mesa Circle, League City, Texas 77573, USA
   5. 437 Garretson Road, Bridgewater, New Jersey 08807, USA

4. The title of the invention is:

   SYNTHESIS OF SEVERELY STERICALLY HINDERED SECONDARY AMINOETHER ALCOHOLS FROM A KETENE AND/OR CARBOXYLIC ACID HALIDE AND/OR CARBOXYLIC ACID ANHYDRIDE

5. The name, registration, customer and telephone numbers of the attorney is:

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Registration Number(s):	47,571	/	29,203
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   Customer Number 27810 Deposit Account No. 05-1330

6. The docket number used to identify this application is: Docket No. JJA-0303

7. Statement as to whether invention was made by an agency of the U.S. Government or under contract with an agency of the U.S. Government;

   This invention was made by an agency of the United States Government, or under contract with an agency of the United States Government.

   [X] No.

   [ ] Yes.

   The name of the U.S. Government agency and the Government contract number are:

8. Identification of documents accompanying this cover sheet:

   A. Documents required by 37 C.F.R. §§ 1.51(c)(2)-(3):

   [X] Specification Number of pages: 36

   [ ] Drawings Number of sheets: ____

   B. Additional documents:

   [X] Claims Number of claims: 22

   [ ] Assignment

   [ ] Other: ____

9. Fee

The filing fee for this provisional application, as set in 37 C.F.R. § 1.16(k), is $ 160.00 for other than a small entity.

10. Method of fee payment

[X] Charge Deposit Account No. 05-1330 in the amount of $ 160.00.
A duplicate of this Cover Sheet is attached.

Date: 16 Feb 2004

Signature of Attorney

Address to which correspondence is to be sent:

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2/16/2004

APPLICATION FOR UNITED STATES PATENT

SYNTHESIS OF SEVERELY STERICALLY HINDERED SECONDARY AMINOETHER ALCOHOLS FROM A KETENE AND/OR CARBOXYLIC ACID HALIDE AND/OR CARBOXYLIC ACID ANHYDRIDE

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Christine N. Elia

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KATHLEEN A. KUNA

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Kathleen A. Kuna

(Signature of person mailing paper or fee)

CASE NO. JJA-0303

27810

PATENT TRADEMARK OFFICE

SYNTHESIS OF SEVERELY STERICALLY HINDERED SECONDARY AMINOETHER ALCOHOLS FROM A KETENE AND/OR CARBOXYLIC ACID HALIDE AND/OR CARBOXYLIC ACID ANHYDRIDE

FIELD OF THE INVENTION

[0001] The present invention relates to a process for the preparation of severely sterically hindered secondary aminoether alcohols.

DESCRIPTION OF RELATED ART

[0002] It is well-known in the art to treat gases and liquids, such as mixtures containing acidic gases including CO_2, H_2S, CS_2, HCN, COS and oxygen and sulfur derivatives of C_1 to C_4 hydrocarbons with amine solutions to remove these acidic gases. The amine usually contacts the acidic gases and the liquids as an aqueous solution containing the amine in an absorber tower with the aqueous amine solution contacting the acidic fluid countercurrently. Usually this contacting results in the simultaneous removal of substantial amounts of both the CO_2 and H_2S. USP 4,112,052, for example, utilizes a sterically hindered amine to obtain nearly complete removal of CO_2 and H_2S acid gases. This process is particularly suitable for systems in which the partial pressures of the CO_2 and related gases are low. For systems where the partial pressure of CO_2 is high or where there are many acid gases present, e.g., H_2S, COS, CH_3SH, CS_2, etc., a process utilizing an amine in combination with a physical absorbent, referred to as a "non-aqueous solvent process" is practiced. Such a system is described in USP 4,112,051.

[0003] Selective removal of H_2S from acid gas systems containing both H_2S and CO_2, however, is very desirable. Such selective removal results in a

relatively high H_2S/CO_2 ratio in the separated acid gas which facilitates the subsequent conversion of the H_2S to elemental sulfur in the Claus process.

[0004] The typical reactions of aqueous secondary and tertiary amines with CO_2 and H_2S can be represented as follows:

$$H_2S + R_3N \rightleftharpoons R_3NH^+ + HS^-$$

$$H_2S + R_2NH \rightleftharpoons R_2NH_2^+ + HS^-$$

$$CO_2 + R_3N + H_2O \rightleftharpoons R_3NH^+ + HCO_3^-$$

$$CO_2 + 2\,R_2NH \rightleftharpoons R_2NH_2^+ + R_2NCO_2^-$$

where R is the same or different organic radical and may be substituted with a hydroxyl group. Because the reactions are reversible they are sensitive to the CO_2 and H_2S partial pressures which is determinative of the degree to which the reactions occur.

[0005] Selective H_2S removal is particularly desirable in systems having low H_2S/CO_2 ratios and relatively low H_2S partial pressures as compared to that of the CO_2. The ability of amine to selectivity remove H_2S in such systems is very low.

[0006] Solutions of primary and secondary amines such as monoethanol-amine (MEA), diethanolamine (DEA), diisopropanolamine (DPA), and hydroxyethoxyethylamine (DEA) absorb both H_2S and CO_2, and thus have proven unsatisfactory for the selective removal of H_2S to the exclusion of CO_2. The CO_2 forms carbamates with such amines relatively easily.

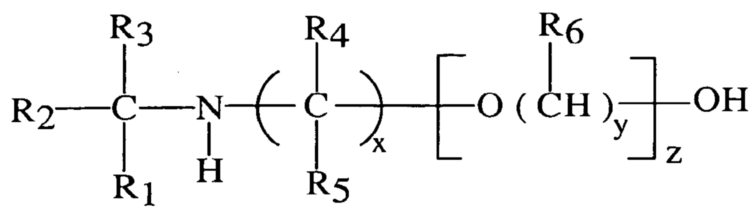
[0007] H_2S has been selectively removed from gases containing H_2S and CO_2 by use of diisopropanolamine (DIPA) either alone or mixed with a non-aqueous physical solvent such as sulfolane. Contact times, however, must be kept short to take advantage of the faster reaction of H_2S with the amine as compared to the rate of CO_2 reaction with the amine.

[0008] Frazier and Kohl, Ind. and Eng. Chem., 42, 2288 (1950) showed that the tertiary amine methydiethanolamine (MDEA) is more selective toward H_2S absorption as compared to CO_2. CO_2 reacts relatively slowly with tertiary amines as compared to the rapid reaction of the tertiary amine with H_2S. However, it has the disadvantage of having a relatively low H_2S loading capacity and limited ability to reduce the H_2S content to the desired level at low H_2S pressures encountered in certain gases.

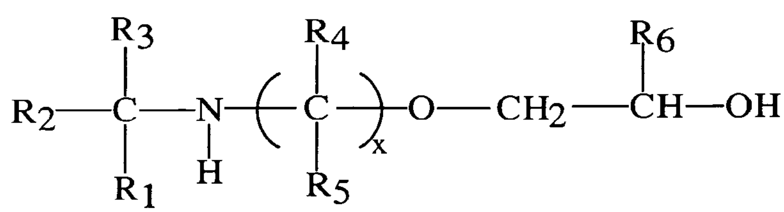
[0009] UK Patent Publication No. 2,017,524A discloses the use of aqueous solutions of dialkylmonoalkanolamines, e.g., diethylmonoethanol amine (DEAE), for the selective removal of H_2S, such material having higher selectivity and capacity for H_2S removal at higher loading levels than MDEA. DEAE, however, has the disadvantage of a low boiling point of 161°C, making it relatively highly volatile resulting in large material loss.

[0010] USP 4,471,138 the entire teaching of which is incorporated herein by reference, teaches severely sterically hindered acyclic secondary aminoether alcohols having a high selectivity for H_2S compared to CO_2. Selectivity is maintained at high H_2S and CO_2 loadings.

[0011] The severely sterically hindered acyclic aminoether alcohols of USP 4,471,138 are represented by the general formula:



wherein R_1 and R_2 are each independently selected from the group consisting of alkyl and hydroxyalkyl radicals having 1-4 carbon atoms, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, and hydroxyalkyl radicals having 1-4 carbon atoms, with the proviso that at least one of R_4 or R_5 bonded to the carbon atom which is directly bonded to the nitrogen atom is an alkyl or hydroxyalkyl radical when R_3 is hydrogen, x and y are each positive integers ranging from 2-4, and z is a positive integer ranging from 1-4. These materials are prepared by a high temperature reaction preferably in the presence of a solvent, of a secondary or tertiary alkyl primary amine with an ether alcohol containing a carbonyl functionality in the presence of a source of hydrogen or with a haloalkoxyalkanol. Preferably the composition is of the general formula:



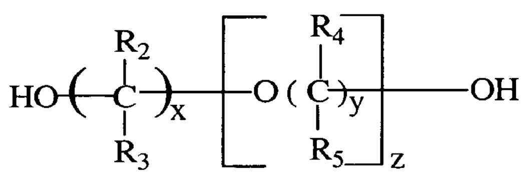
wherein:

$R_1 = R_2 = R_3 = CH_3$-; $R_4 = R_5 = R_6 = H$;
$R_1 = R_2 = R_3 = CH_3$-; $R_4 = H$ or CH_3; $R_5 = R_6 = H$;
$R_1 = R_2 = R_3 = R_6 = CH_3$-; $R_4 = R_5 = H$;
$R_1 = R_2 = R_3 = CH_3CH_2$-; $R_4 = R_5 = R_6 = H$; or
$R_1 \neq R_2 \neq R_3 = H, CH_3$-, CH_3CH_2-; $R_4 \neq R_5 \neq R_6 = H, CH_3$-;
and where x = 2 or 3.

[0012] U.S. Patent 4,487,967 is directed to a process for preparing severely sterically hindered secondary aminoether alcohols by reacting a primary amino compound with a polyalkenyl ether glycol in the presence of a hydrogenation catalyst at elevated temperatures and pressures. The primary amino compounds employed have a general formula:

$$R^1\text{—}NH_2$$

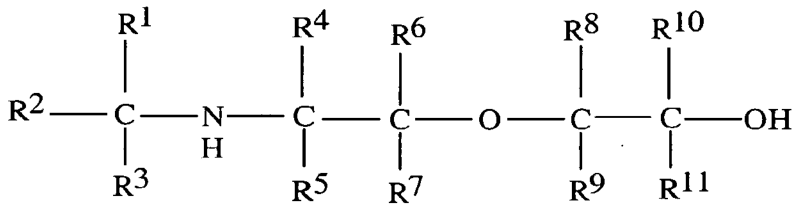
where R^1 is selected from the group consisting of secondary or tertiary alkyl radicals having 3 to 8 carbon atoms or cycloalkyl radicals having 3 to 8 carbon atoms. The polyalkenyl ether glycols employed have the general formula:



where R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl radicals, and C_3-C_8 cycloalkyl radicals, with the proviso that if the carbon atom of R_1 directly attached to the nitrogen atom is secondary, at least one of R_2 and R_3 directly bonded to the carbon which is bonded to the hydroxyl group is as alkyl or cycloalkyl radical, x and y are each positive integers independently ranging from 2 to 4 and z is from 1 to 10, preferably 1 to 6, more preferably 1 to 4. The process is carried out in the presence of a catalytically effective amount of a supported Group VIII metal containing hydrogenation catalyst at elevated temperatures and pressure and the mole ratio of amino compound to polyalkenyl ether glycol is less than 2:1 when z is greater than 1.

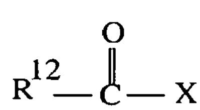
SUMMARY OF THE INVENTION

[0013] Severely sterically hindered secondary aminoether alcohols of the general formula **1**

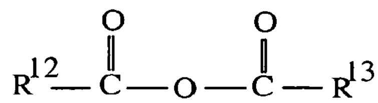


1

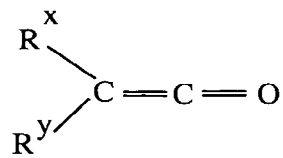
wherein R^1 and R^2 are each independently selected from the group consisting of alkyl and hydroxyalkyl radicals having 1 to 4 carbon atoms, preferably 1 to 2 carbon atoms, or R^1 and R^2 in combination with the carbon atom to which they are attached form a cycloalkyl group having 3 to 8 carbons; R^3 is selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbon atoms, and mixtures thereof, preferably 1 to 2 carbon atoms, preferably alkyl or hydroxyalkyl radicals having 1 to 4 carbon atoms, more preferably 1 to 2 carbon atoms; R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are the same or different and are selected from hydrogen, alkyl or hydroxyalkyl radicals having 1 to 4 carbon atoms, preferably 1 to 2 carbon atoms, or cycloalkyl radicals having 3 to 8 carbons; R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are preferably hydrogen provided that when R^3 is hydrogen at least one of R^4 and R^5 bonded to the carbon which is directly bonded to the nitrogen atom is an alkyl or hydroxyalkyl radical, are prepared by a process involving reacting an organic carboxylic acid halide, an organic carboxylic acid anhydride or a ketene, or a mixture of any two or of all three thereof, of the formula **2**:



2a

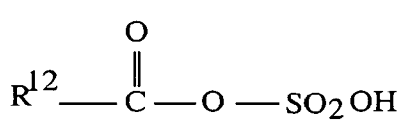


2b

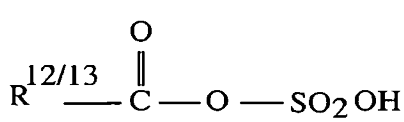


2c

wherein R^{12} and R_{13} are the same or different and each is selected from the group consisting of alkyl radicals having 1 to 4 carbon atoms, preferably 1 to 2 carbon atoms, most preferably methyl, or aryl radicals, preferably phenyl substituted with hydrogen, one or more alkyl radicals having 1-10 carbon atoms, preferably 1-4 carbon atoms, most preferably methyl in the para position, and mixtures thereof, and x is a halogen selected from the group consisting of F, Cl, Br, I and mixtures thereof, preferably Cl, and wherein R^x and R^y are the same or different and are selected from the group consisting of hydrogen, alkyl radicals having 1-4 carbons, preferably 1 to 2 carbons, aryl radicals, preferably aryl radicals bearing substituents selected from the group consisting of hydrogen and one or more alkyl radicals having 1 to 10 carbons, preferably 1-4 carbons, and mixtures thereof, or R^x and R^y in combination with the carbon to which they are attached form a cycloalkyl radical having 3 to 8 carbons, preferably R^x and R^y are hydrogen or phenyl, with 50% to fuming, preferably 75% to fuming, more preferably 90% to fuming sulfuric acid to produce monoacyl sulfate **3** and/or diacyl sulfate **4**:



3a



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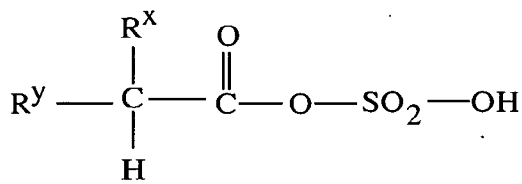

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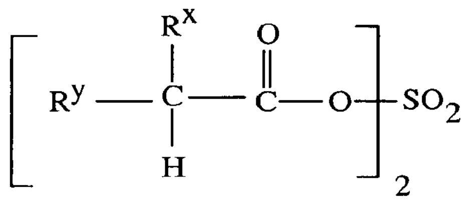

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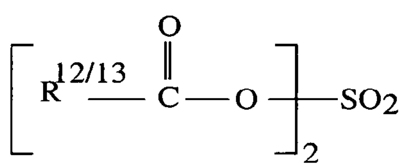
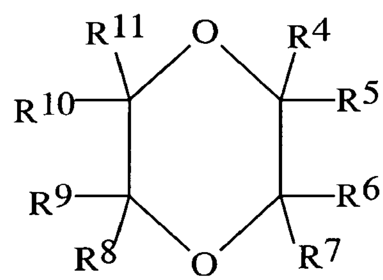


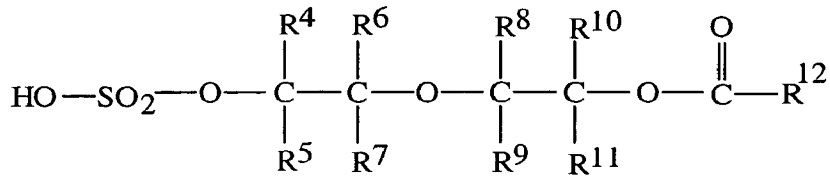
4b

wherein $R^{12/13}$ means that in the product the R group can be R^{12} or R^{13}, or mixtures thereof, which are then reacted with a 1,4-dioxane of the formula **5**:

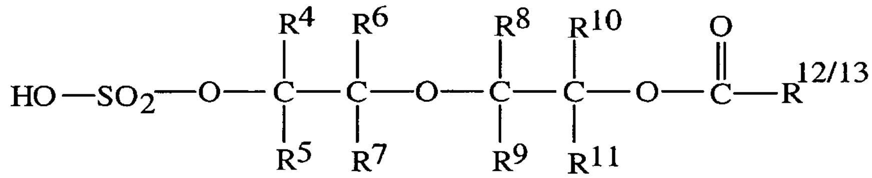


5

wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are the same or different and are selected from hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons, and mixtures thereof, preferably 1-2 carbons, and mixtures thereof, more preferably R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are hydrogen, to yield material of the general formula **6** and/or **7**:



6a



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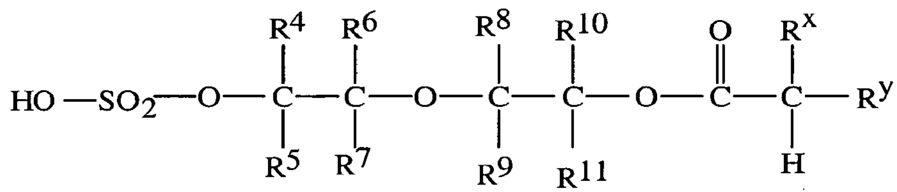

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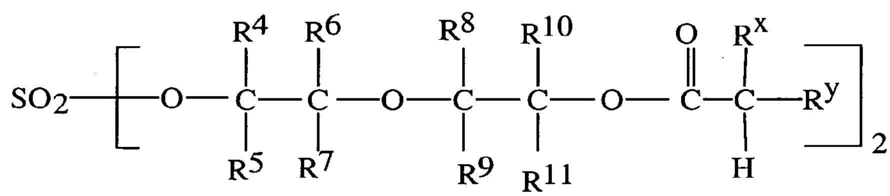
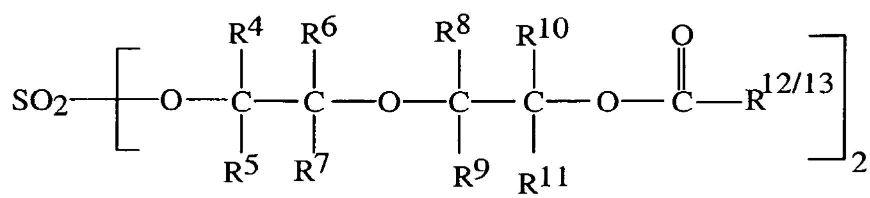


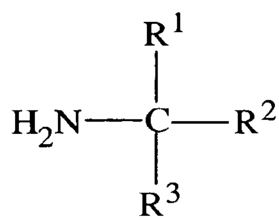
7a



7b

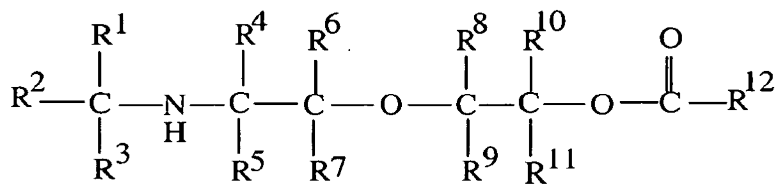
or mixtures thereof. It is not necessary that the product from each reaction step be isolated before being reacted with the reactant of a subsequent reaction step up to this point. A cleavage product is produced. The mixing of the organic carboxylic acid halide, organic carboxylic acid anhydride, ketene or mixture thereof, with the sulfuric acid and the dioxane can be in any order or sequence. Thus, the anhydride, and halide, ketene or mixture thereof, can be mixed with

the sulfuric acid and then mixed with the dioxane, or the dioxane can be first mixed with the sulfuric acid and then the anhydride, acid halide, ketene, or mixture thereof, can be added, or the anhydride, acid halide, ketene or mixture thereof can be mixed with the dioxane followed by the addition of the sulfuric acid. Thus, the combination of the anhydride, acid halide, ketene or mixture thereof with the dioxane and the sulfuric acid can be combined into a single reaction mixture and reacted as a mixture resulting in the one step production of the desired cleavage product. This cleavage product is then aminated using an alkyl amine of the formula **8**

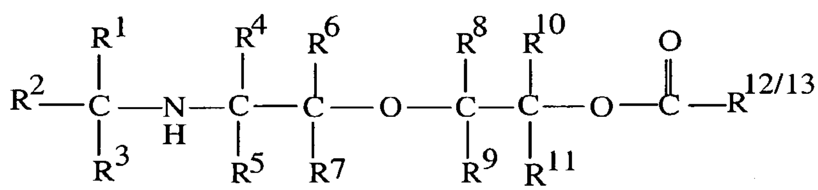


8

wherein R^1 and R^2 are the same of different and selected from the group consisting of alkyl and hydroxyalkyl radicals having 1 to 4 carbon atoms, and mixtures thereof, preferably 1 to 2 carbon atoms, more preferably methyl, or R^1 and R^2 in combination with the carbon atom to which they are attached form a cycloalkyl group having 3 to 8 carbons, and mixtures thereof; R^3 is selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbon atoms, and mixtures thereof, preferably 1 to 2 carbon atoms, preferably alkyl or hydroxyalkyl radicals having 1 to 4 carbon atoms, more preferably 1 to 2 carbon atoms, most preferably methyl, provided that when R^3 is hydrogen then at least one of R^4 and R^5 is an alkyl or hydroxyalkyl radical, to yield material of the general formula **9**:



9a



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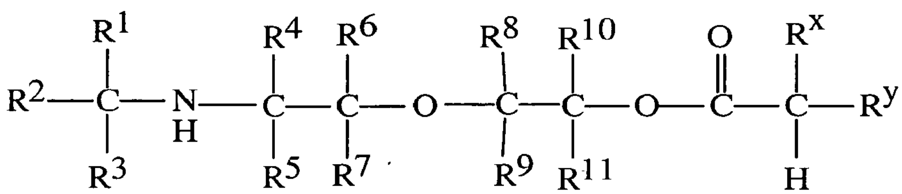
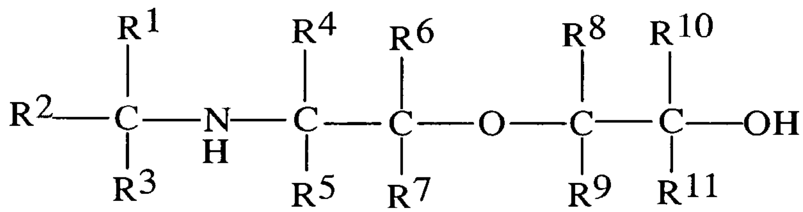


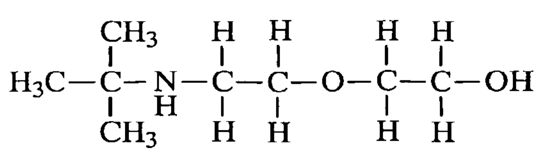
9c

or mixtures thereof, which is then hydrolyzed with base to yield **1**:

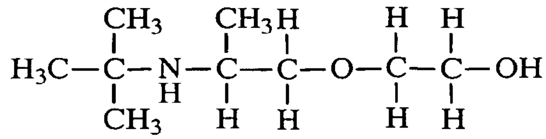


1

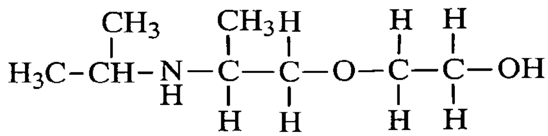
[0014] The preferred compounds defined by the general formula **1** include:



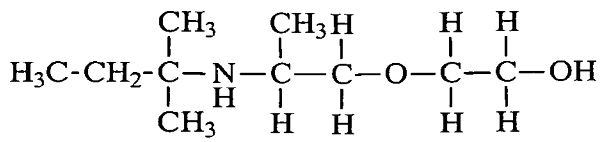
2-(2-*tert*-butylaminoethoxy)ethanol,



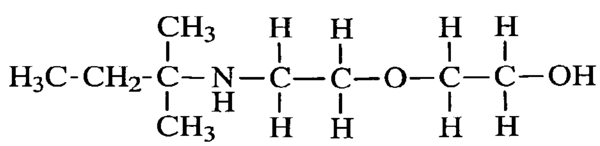
2-(2-*tert*-butylaminopropoxy)ethanol,



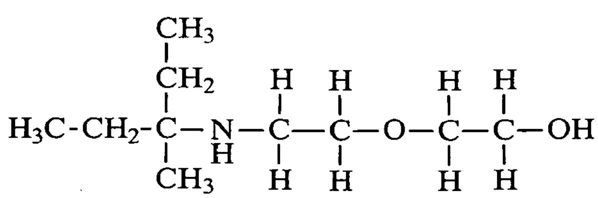
2-(2-isopropylaminopropoxy)ethanol,



2-[2-(1,1-dimethylpropylamino)propoxy]ethanol,

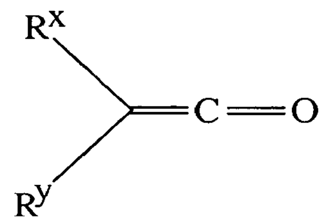


2-[2-(1,1-dimethylpropylamino)ethoxy]ethanol,



2-[2-(1-ethyl-1-methylpropylamino)ethoxy]ethanol.

[0015] Typical starting materials are ketenes represented by the formula **2**:



2

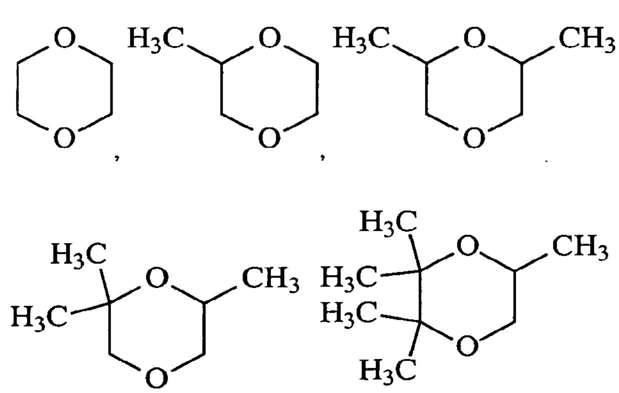
wherein R^x and R^y are the same or different and are selected from the group consisting of hydrogen, alkyl radicals having from 1 to 4 carbons, preferably 1 to 2 carbons, most preferably hydrogen, aryl radicals, preferably aryl radicals bearing substituents selected from the group consisting of hydrogen, one or more alkyl radicals having 1 to 10 carbons, preferably 1 to 4 carbons, and mixtures thereof, or R^x and R^y in combination with the carbon to which they are attached form a cycloalkyl radical having 3 to 8 carbons, and mixtures thereof, preferably R^x and R^y are hydrogen or phenyl.

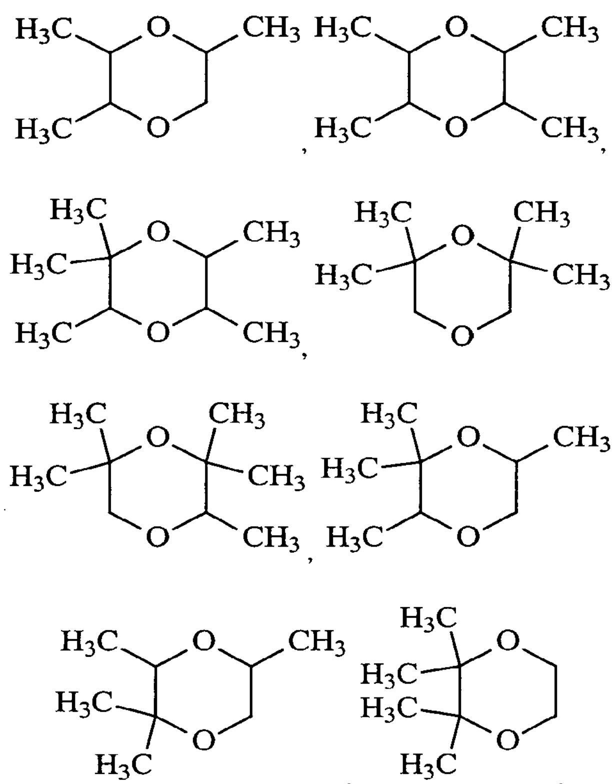
[0016] The ketenes useful in the present invention can be prepared employing any of the processes typical in the art. Thus, for example, acetic acid can be subjected to high temperature dehydration in the presence of $AlPO_4$, or acetone can be subjected to pyrolysis at from 500-750°C to yield ketene and methane.

[0017] The ketene, organic carboxylic acid halide, organic carboxylic acid anhydride, or mixtures of any two or all three thereof, is reacted with 50% to fuming, preferably 75% to fuming, most preferably 90% to fuming sulfuric acid, H_2SO_4, at preferably a 1:1 molar ratio to form the monoacyl sulfate **3** or in about a 2:1 molar ratio to form the diacyl sulfate **4**. Excess sulfuric acid can be used at the practitioners discretion, but the use of excess acid would necessitate the practice of an additional separation step. The use of about a stoichiometric ratio, therefore, is preferred. The use of concentrated sulfuric acid (90% to fuming) is preferred. Fuming sulfuric acid I also known as oleum. It is a

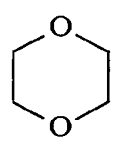
solution of sulfur trioxide in 100% sulfuric acid. 100% sulfuric acid is also referred to as monohydrate because it constitutes one molecule of SO_3 combined with one molecule of H_2O. The percent of free SO_3 is used as a measure of oleum or fuming sulfuric acid strength. Thus, 20% fuming sulfuric acid constitutes 20% free SO_3 over and above the 100% sulfuric acid carrier solvent. Twenty (20) % fuming sulfuric acid contains 20% SO_3 and 80% H_2SO_4 (of 100% concentrated H_2SO_4) by weight. Oleum or fuming sulfuric acid can contain as high as 80%+ free SO_3. Reaction can be conducted at about -80°C to about 150°C, preferably about -20°C to about 125°C at a pressure between about 1 bar to 100 bars, preferably about 1 bar to 50 bars, more preferably about 1 bar to 10 bars. The reaction can be carried out in an inert solvent such as sulfolane, hexanes, acetonitrile. Preferably the dioxane for the subsequent cleavage reaction is used as the solvent resulting in a unified first step wherein the reaction mixture contains the carboxylic acid halide, the organic carboxylic acid anhydride, the ketene or mixture thereof, the sulfuric acid and the dioxane. This reaction mixture is then reacted under the condition subsequently described for the dioxane cleavage reaction.

[0018] Acyl sulfate **3** or **4** is then reacted with a dioxane **5** which is typically of the formula:





Other substituted isomers can be readily envisioned. Preferably, the dioxane is



Cleavage of the dioxane ring and reaction is for a time sufficient to achieve about 60-90% conversion to product.

[0019] The reaction can be carried out either in the absence of solvent, in which case the dioxane serves as the solvent for the reaction, or in a solution containing an additional inert solvent such as acetonitrite or toluene, the reaction being conducted at temperatures of from about -80°C to about 200°C.

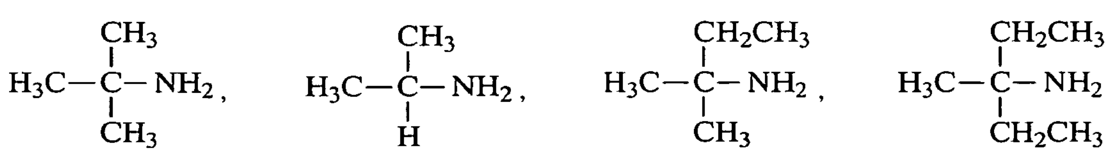
[0020] Preferably, the dioxane serves as the solvent for the reaction. The molar ratio of dioxane to acyl sulfate, for the reaction of dioxane with acyl

sulfate **3** is about 1:1 to about 10:1, preferably about 1:1 to about 8:1, most preferably about 1:1 to about 5:1, while the molar ratio of dioxane to acyl sulfate of formula **4** is about 2:1 to about 10:1, preferably about 2:1 to about 8:1, more preferably about 2:1 to about 5:1. Expressed differently, the dioxane to acyl sulfate ratio is about stoichiometric to about 10:1, preferably about stoichiometric to about 8:1, more preferably about stoichiometric to about 5:1. The temperature for the reaction of dioxane with acyl sulfate of general formula **3** is in the range of between about -80°C to about 200°C, preferably about -20°C to about 160°C, most preferably about -20°C to about 50°C, and the temperature for the reaction of dioxane with the acyl sulfate of general formula **4** is in the range of between about 50°C to about 200°C, preferably about 70°C to about 160°C, more preferably about 80°C to about 140°C.

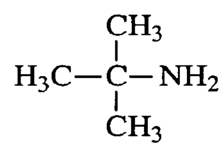
[0021] The ether cleavage process is described in greater detail by Karger and Mazur in "The Cleavage of Ethers by Mixed Sulfonic-Carboxylic Anhydrides", Journal of the American Chemical Society, 1968, 90, 3878-3879. See also, "Mixed sulfonic-carboxylic anhydrides. I. Synthesis and thermal stability. New syntheses of sulfonic anhydrides" Journal of Organic Chemistry, 1971, 36, 528; and "Mixed sulfonic-carboxylic anhydrides. II. Reactions with aliphatic ethers and amines" Journal of Organic Chemistry, 1971, 36, 532.

[0022] The reaction of a dioxane **5** with acyl sulfate **3** yields cleavage product of general formula **6,** while the reaction of a dioxane **5** with diacyl sulfate **4** yields a cleavage product of the formula **7**.

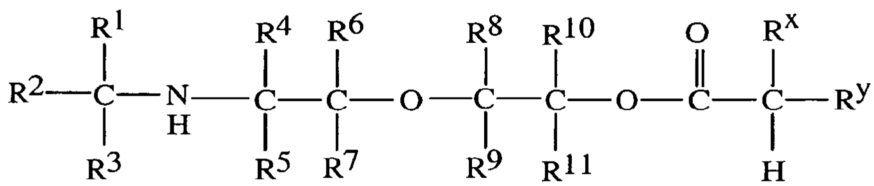
[0023] The cleavage products **6** and **7** are then aminated using an amine **8**, typically of the formulae:



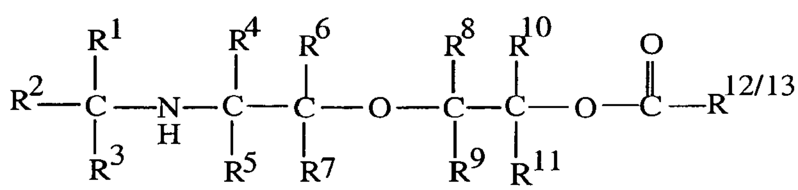
preferably:



for a time sufficient to replace the sulfate group in cleavage products **6** and **7** with an amine **8**. In the case of the amination of cleavage product **7**, at least two moles of the amine **8** are required for each mole of **7**. In general, the amine to cleavage product sulfonate group mole ratio is in the range of about stoichiometric to about 10:1, preferably about stoichiometric to about 8:1, more preferably about stoichiometric to about 4:1. In the case of the amination of either product **6** or product **7**, the same aminated product **9** is produced:



9a



9b

[0024] This amination step can be carried out under any conditions typical in the art. Amination can be conducted at atmosphere or at elevated pressure, elevated pressure being especially suitable when amination is to be performed using relatively low boiling amines such at t-butylamine.

[0025] Thus, amination can be conducted at pressures of from about atmospheric (1 bar) to about 100 bars, preferably about 1 to about 50 bars and at temperatures of from about 40°C to about 200°C, preferably about 40°C to about

125°C. The process can be performed under reflux but this is not absolutely necessary. An inert solvent optionally can be used such as benzene, toluene, diethyl ether, hexanes, and the like.

[0026] This aminated product **9** is hydrolyzed to product **1** using a base, which is typically an alkali metal hydroxide, alkali metal carbonate, alkali metal alkoxide, such as sodium hydroxide, sodium carbonate, sodium methoxide, sodium tert-butoxide, etc. Reaction is conducted at about 20°C to about 110°C, preferably about 20°C to about 50°C. The process can be conducted under reflux. Solvents which can be used if either necessary or simply desirable include water and alcohols and mixtures thereof. The alcohol can be the same as that from which the alkoxide base is derived, i.e., methanol in the solvent for alkali metal methoxide.

EXAMPLES

[0027] The preparation of 2-(2-*tert*-butylaminoethoxy)ethanol (EETB). A 100 mL one-necked flask was charged with 1,4-dioxane (20 g, 0.23 mol, 20 mL) under a nitrogen atmosphere; acetic anhydride (4 mL, 4.28 g, 42 mmol) was added followed by the addition of 20% fuming sulfuric acid (1.04 mL, 2.0 g; contains 16.4 mmol of H_2SO_4) at room temperature. The reaction mixture was refluxed at 101°C and checked by NMR. The ^{1}H NMR spectrum showed that products of cleavage reached a maximum after 18 h. The reaction mixture was evaporated under vacuum to dryness (bath 50°C, 15 mm of Hg). Toluene (50 mL) was added to the residue followed by the addition of *tert*-butylamine (30 mL, 21 g, 0.29 mol) at room temperature. The reaction mixture was gently (*tert*-butylamine BP = 44–46°C) refluxed for 30 h. Then, the reaction mixture was cooled to room temperature and filtered; the precipitate was washed with toluene. The filtrate was partially evaporated under vacuum to remove *tert*-butylamine. The residue was filtered and the precipitate was washed with

toluene. The filtrate was evaporated under vacuum to give a yellow residual oil (4.5 g). The NMR spectra showed 2-(2-*t*-butylaminoethoxy)ethyl acetate of 60-70% purity. The character of signals in ^1H NMR spectrum suggests 2-(2-hydroxyethoxy)ethyl acetate as major impurity (signal of acetoxy group: singlet at 2.09 ppm, of etheral signals: m, 3.65–3.72 ppm, and ester signal: m, 4.21–4.27 ppm), as result of incomplete amination or hydrolysis during work up.

[0028] The reflux of 2-(2-*t*-butylaminoethoxy)ethyl acetate (2 g, 10 mmol) with 15 mmol of NaOH in methanol (10 mL) for 6 h followed by evaporation under vacuum, extraction with diethyl ether and removing of solvent under vacuum gave 1.6 g of yellow oil, the NMR of which confirmed 2-(2-*tert*-butylaminoethoxy)ethanol (EETB) of 70–75% purity. The EETB is probably contaminated with diethylene glycol (extra protons in the range 3.59–3.73 ppm; by comparison with NMR data for diethylene glycol: 3.60 ppm, m, 4H; 3.74 ppm, m, 4H).

[0029] <u>The cleavage of 1,4-dioxane with diaetyl sulfate generated from fuming sulfuric acid and a twofold excess of acetic anhydride</u>. The same reaction conditions were used as for the cleavage above using 20% fuming sulfuric acid and acetic anhydride (twofold excess: 1 equivalent for SO_3, plus 2 equivalent for H_2SO_4, and plus 100% excess). Also, the amination with *t*-$BuNH_2$ was carried out in an autoclave (bomb) to provide maximum completeness.

[0030] A 100 mL one-necked flask was charged with 1,4-dioxane (30 g, 0.35 mol, 30 mL) under a nitrogen atmosphere; acetic anhydride (7.1 mL, 7.66 g, 75 mmol was added followed by the addition of 20% fuming sulfuric acid (1.04 mL, 2.0 g; contains 0.4 g, 5.0 mmol of SO_3 and 1.6 g, 16.4 mmol of H_2SO_4) at room temperature. The reaction mixture was refluxed for 40 h and checked by

NMR. The ^{1}H NMR spectrum showed the presence of products of cleavage. Reflux was continued for an additional 8 h. The NMR showed the same set of signals as after 40 h. The reaction mixture was evaporated under vacuum to dryness (the reaction mixture was protected from contact with moisture; the solvent was directly evaporated into a dry-ice trap using a dry membrane-type vacuum pump; bath 50°C, 5 mm of Hg). Toluene (50 mL) was added to the residue followed by the addition of *tert*-butylamine (30 mL, 21 g, 0.29 mol) at room temperature. The reaction mixture was stirred for 5 min and the reaction mixture was transferred into an autoclave (bomb) and stirred at approximately 170°C (175–180°C in the oil bath) for 13 h. The reaction mixture was cooled to room temperature and filtered from the precipitate. The precipitate was washed with toluene and the combined filtrate was evaporated in vacuum. Toluene was added to the residue and the mixture was washed with an aqueous solution of sodium carbonate. The organic layer was dried over magnesium sulfate and the solvent was evaporated in vacuum to give 3.4 g of yellow oil. The ^{1}H NMR analysis showed the desired 2-(2-t-butylaminoethoxy)ethylacetate product in 70-75% purity. As in the previous reaction, the major byproduct is 2-(2-hydroxyethoxy)ethyl acetate; extra protons at 2.09 ppm (0.7 H, Ac), 3.58-3.72 (3H) and 4.20–4.24 (0.45 H, CH_2OAc). Part of this product crystallized as colorless needles).

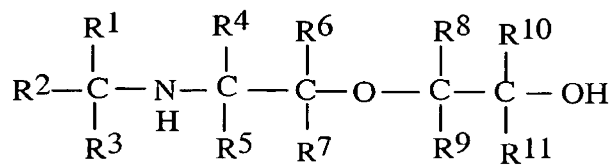
[0031] <u>Cleavage of 1,4-dioxane with diacetyl sulfate generated from fuming sulfuric acid and acetic anhydride (1 equivalent of acetic anhydride for SO_3, plus 2 equivalent for H_2SO_4) at 120°C</u>. A 15 mL sealed tube was charged with 1,4-dioxane (10 g, 0.11 mol, 10 mL) and acetic anhydride (2.67 mL, 2.88 g, 28.2 mmol) was added followed by the addition of 20% fuming sulfuric acid (0.78 mL, 1.5 g; contains 0.3 g, 3.75 mmol of SO_3 and 1.2 g, 12.23 mmol of H_2SO_4) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at 120-122°C for 24 hours and checked by NMR. The ^{1}H NMR spectrum

showed presence of products of cleavage. The reaction mixture was evaporated under vacuum to dryness. Toluene (50 mL) was added to the residue followed by the addition of *tert*-butylamine (17 mL, 11.8 g, 0.16 mol) at room temperature. The reaction mixture was gently refluxed for 24 h, cooled to room temperature and filtered from the precipitate. The precipitate was washed with toluene and the combined filtrates were evaporated under vacuum. Toluene was added to the residue and the mixture was washed with an aqueous solution of sodium carbonate. The organic layer was dried over magnesium sulfate and the solvent was evaporated under vacuum to give 3.5 g of brown oil. The ^{1}H NMR analysis showed the desired product 2-(2-*tert*-butylaminoethoxy)ethyl acetate of approximately 70% purity. The major by-products are 2-(2-hydroxyethoxy)ethyl acetate or 2-(2-acetoxyethoxy)ethyl acetate.

[0032] <u>Cleavage of 1,4-dioxane with diacetyl sulfate generated from sulfur trioxide and acetic anhydride</u>. A 15 mL sealed tube was charged with dioxane (10 g, 0.115 mol), acetic anhydride (1.81 mL, 1.96 g, 19 mmol), and sulfur trioxide (1.54 g, 19 mmol) under a nitrogen atmosphere. The mixture was stirred at 119-123°C for 5 h (brown clear solution). The ^{1}H NMR analysis showed characteristic signals of cleavage products. The reaction mixture was concentrated under vacuum. The residue was stirred with *tert*-butyl amine (20 mL, 13.92 g, 0.19 mol) in toluene (30 mL) under gentle reflux for 24 h. The reaction mixture was cooled to room temperature, filtered, and the precipitate was washed with toluene. The filtrate was evaporated and the product was extracted with toluene. The extract was evaporated under vacuum to give 2 g of yellow - brown oil. The NMR test showed desired product 2-(2-*tert*-butylaminoethoxy)ethyl acetate of approximately 65% purity.

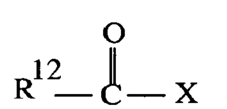
WHAT IS CLAIMED IS:

1. A method for the synthesis of severely sterically hindered secondary aminoether alcohols of the formula

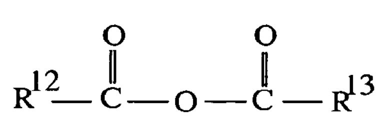


(1)

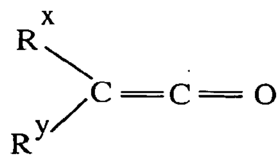
wherein R^1 and R^2 are each selected from the group consisting of alkyl, hydroxylalkyl radicals having 1 to 4 carbon atoms or in combination with the carbon atom to which they are attached they form a cycloalkyl group having 3 to 8 carbon atoms, and R^3 is selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbon atoms, and mixtures thereof, and R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are the same or different and are selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons provided that at least one of R^4 or R^5 bonded to the carbon atom directly bonded to the nitrogen atom is an alkyl or hydroxyalkyl radical when R^3 is hydrogen, the process involving reacting an organic caraboxylic acid halide, an organic carboxylic acid anhydride, a ketene, or a mixture of any two or of all three thereof, of the formula



2a

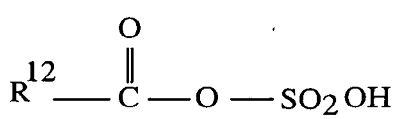


2b

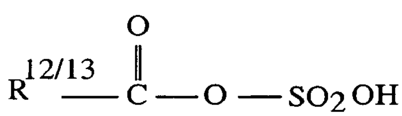


2c

wherein R^{12} and R^{13} are the same or different and are selected from the group consisting of alkyl radicals having 1 to 4 carbon atoms, aryl radicals bearing hydrogen or C_1 to C_{10} alkyl radicals substituted thereon, and mixtures thereof, X is a halogen selected from the group consisting of F, Cl, Br, I , and mixtures thereof, and R^x and R^y are the same or different and are selected from the group consisting of hydrogen, alkyl radicals having 1-4 carbons, aryl radicals, aryl radicals bearing substituents selected from the group consisting of hydrogen and one or more alkyl radicals having 1 to 10 carbons, and mixtures thereof, or R^x and R^y in combination with the carbon to which they are attached form a cycloalkyl radical having 3 to 8 carbons, with 50% to fuming sulfuric acid to yield monoacylsulfate (3) and/or diacylsulfate (4) of the formula



3a



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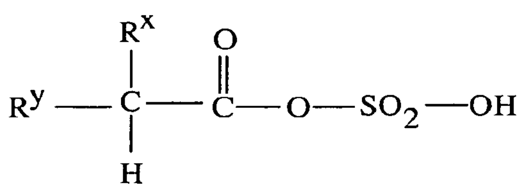
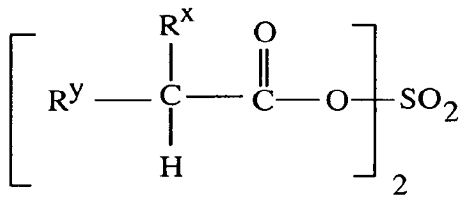


3c



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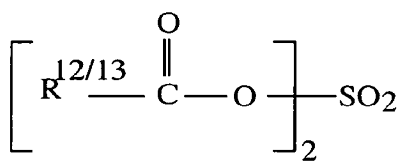
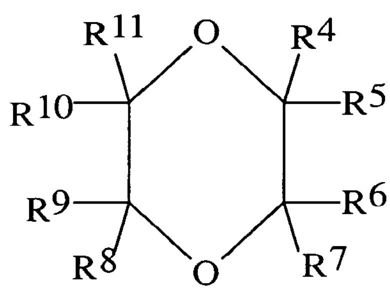


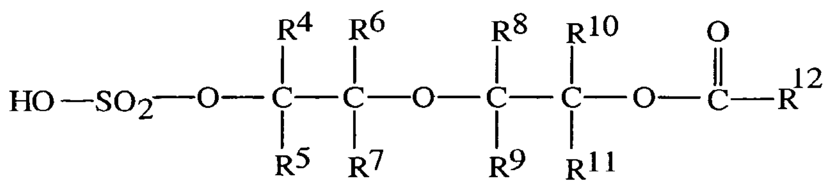
4b

which is then reacted with a dioxane of the formula



5

wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are the same or different and are selected from hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons to yield products of the structure **6** and/or **7**:



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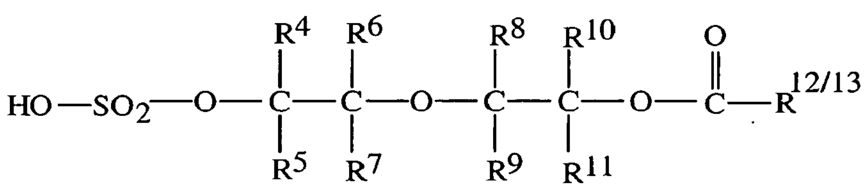

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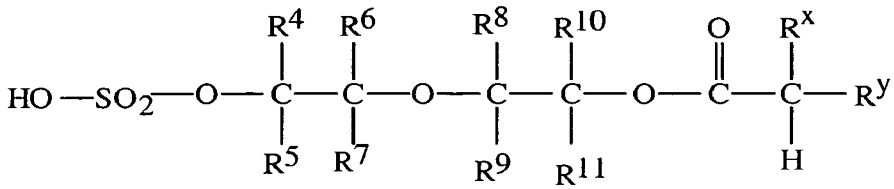

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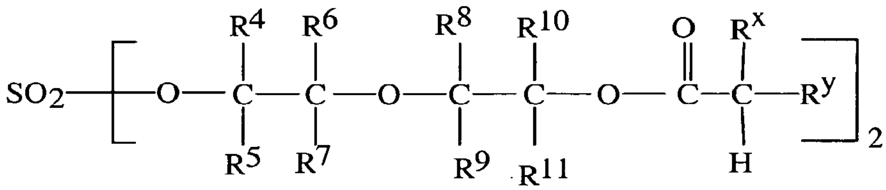
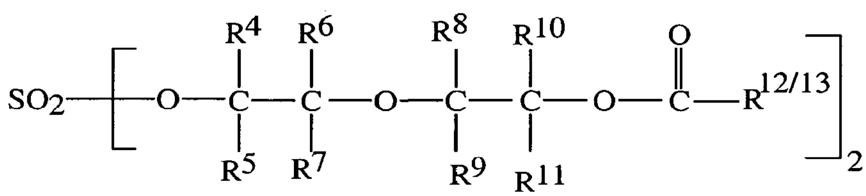
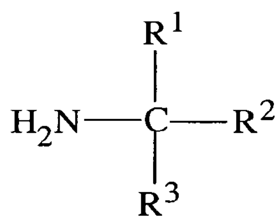


7a



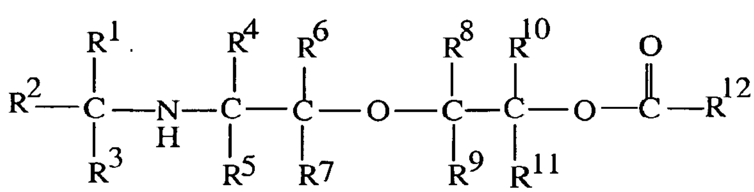
7b

and mixtures thereof, which are then aminated with an alkyl amine of the formula



8

wherein R^1, R^2 and R^3 are as previously defined to yield material of the general formula **9**



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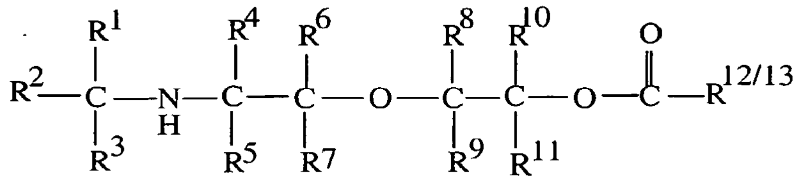

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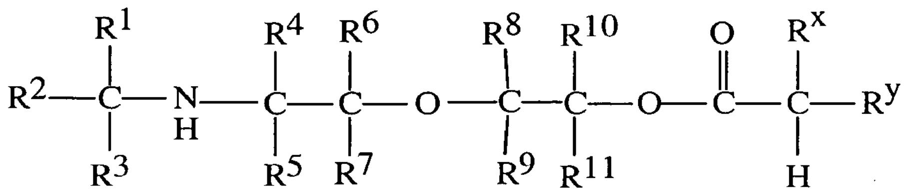


9c

or mixtures thereof, which is then hydrolyzed with base to yield product (1).

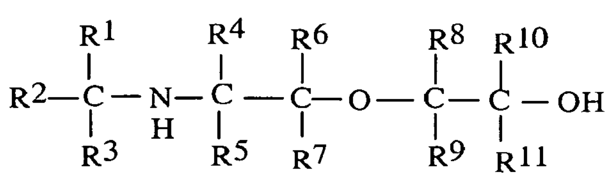
2. The method of claim 1 wherein R^1, R^2, and R^3 are methyl radicals.

3. The method of claim 1 wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are hydrogen, and R^x and R^y are hydrogen or phenyl.

4. The method of claim 1 wherein the base is selected from alkali metal hydroxide, alkali metal alkoxide, or alkali metal carbonate.

5. The method of claim 1 wherein R^1, R^2, and R^3 are methyl, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are hydrogen and R^x and R^y are hydrogen or phenyl.

6. A method for the synthesis of severely sterically hindered secondary aminoether alcohols of the formula



(1)

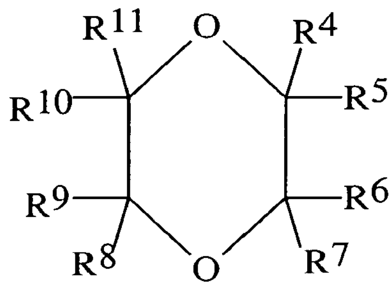
wherein R^1 and R^2 are each selected from the group consisting of alkyl, hydroxylalkyl radicals having 1 to 4 carbon atoms or in combination with the carbon atom to which they are attached they form a cycloalkyl group having 3 to 8 carbon atoms, and R^3 is selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbon atoms, and mixtures thereof, and R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are the same or different and are selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons provided that at least one of R^4 or R^5 bonded to the carbon atom directly bonded to the nitrogen atom is an alkyl or hydroxyalkyl radical when R^3 is hydrogen, the process involving reacting an organic caraboxylic acid halide, of the formula

$$R^{12}-\overset{\overset{\displaystyle O}{\|}}{C}-X \qquad\qquad \text{2a}$$

wherein R^{12} is selected from the group consisting of alkyl radicals having 1 to 4 carbon atoms, aryl radicals bearing hydrogen or C_1 to C_{10} alkyl radicals substituted thereon, and mixtures thereof, and X is a halogen selected from the group consisting of F, Cl, Br, I, and mixtures thereof, with sulfuric acid to yield monoacylsulfate (3) of the formula

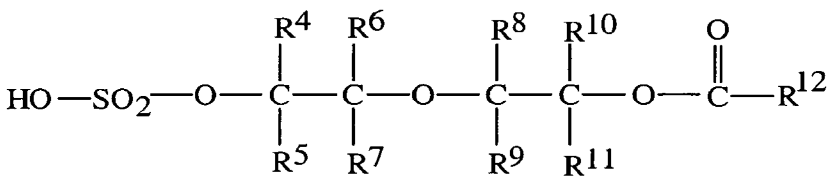
$$R^{12}-\overset{\overset{\displaystyle O}{\|}}{C}-O-SO_2OH \qquad\qquad \text{3a}$$

which is then reacted with a dioxane of the formula



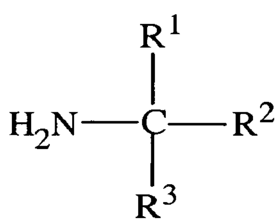
5

wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are the same or different and are selected from hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons to yield products of the structure **6**:



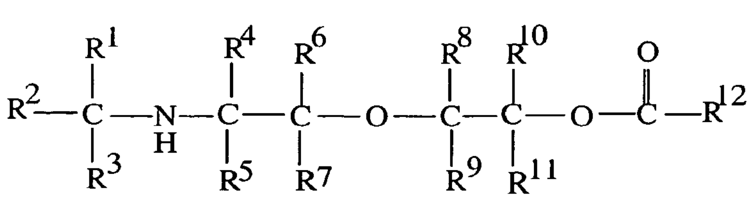
6a

which is then aminated with an alkyl amine of the formula



8

wherein R^1, R^2 and R^3 are as previously defined to yield material of the general formula **9**



9

or mixtures thereof, which is then hydrolyzed with base to yield product (1).

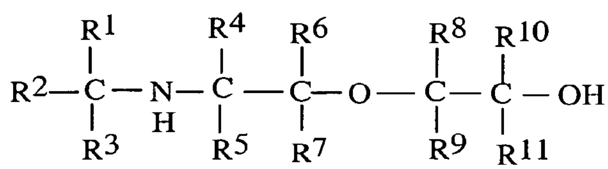
7. The method of claim 6 wherein R^1, R^2, and R^3 are methyl radicals.

8. The method of claim 6 wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are hydrogen.

9. The method of claim 6 wherein the base is selected from alkali metal hydroxide, alkali metal alkoxide, or alkali metal carbonate.

10. The method of claim 6 wherein R^1, R^2, and R^3 are methyl, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are hydrogen.

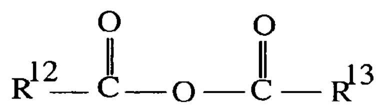
11. A method for the synthesis of severely sterically hindered secondary aminoether alcohols of the formula



(1)

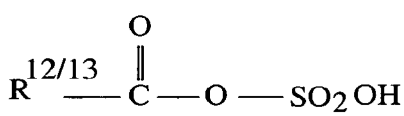
wherein R^1 and R^2 are each selected from the group consisting of alkyl, hydroxylalkyl radicals having 1 to 4 carbon atoms or in combination with the carbon atom to which they are attached they form a cycloalkyl group having 3 to 8 carbon atoms, and R^3 is selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbon atoms, and mixtures thereof, and R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are the same or different and are selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons provided that at least one of R^4 or R^5 bonded to the carbon atom directly bonded to the nitrogen atom is an alkyl or hydroxyalkyl radical when R^3

is hydrogen, the process involving reacting an organic caraboxylic acid anhydride

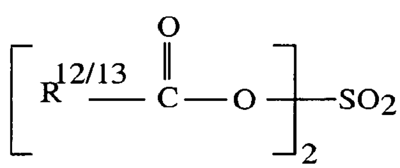


2b

wherein R^{12} and R^{13} are the same or different and each is selected from the group consisting of alkyl radicals having 1 to 4 carbon atoms, aryl radicals bearing hydrogen or C_1 to C_{10} alkyl radicals substituted thereon, and mixtures thereof, with sulfuric acid to yield monoacylsulfate (3) and/or diacylsulfate (4) of the formula

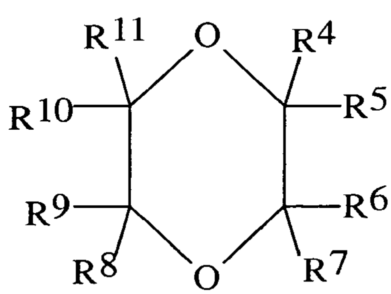


3b



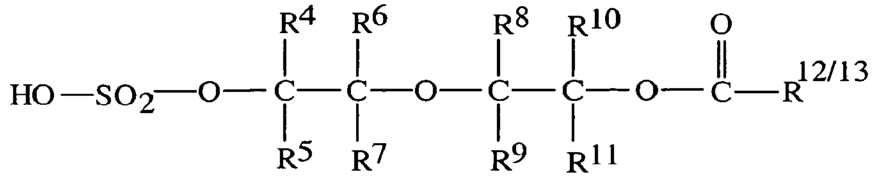
4b

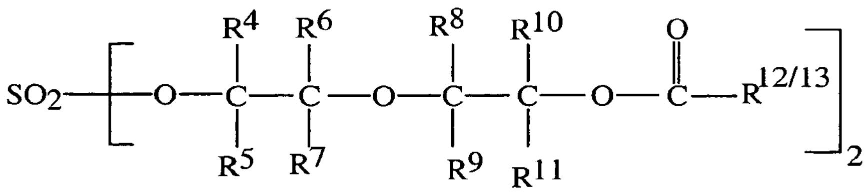
which is then reacted with a dioxane of the formula



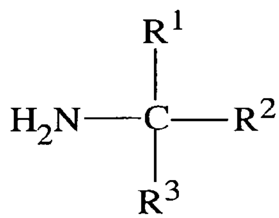
5

wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are the same or different and are selected from hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons to yield products of the structure **6** and/or **7**:

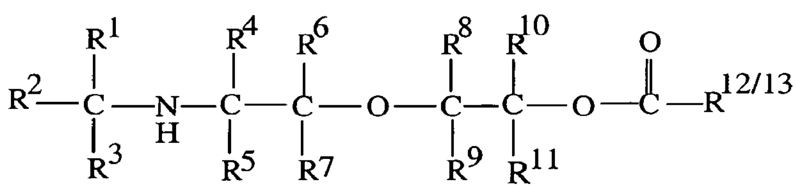

6b


7b

and mixtures thereof, which is then aminated with an alkyl amine of the formula


8

wherein R^1, R^2 and R^3 are as previously defined to yield material of the general formula **9**


9b

which is then hydrolyzed with base to yield product (1).

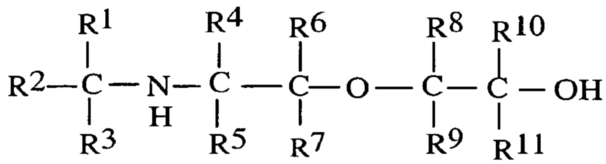
12. The method of claim 11 wherein R^1, R^2, and R^3 are methyl radicals.

13. The method of claim 11 wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are hydrogen.

14. The method of claim 11 wherein the base is selected from alkali metal hydroxide, alkali metal alkoxide, or alkali metal carbonate.

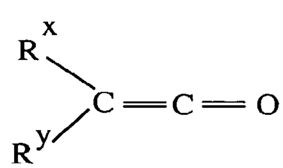
15. The method of claim 11 wherein R^1, R^2, and R^3 are methyl, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are hydrogen.

16. A method for the synthesis of severely sterically hindered secondary aminoether alcohols of the formula



(1)

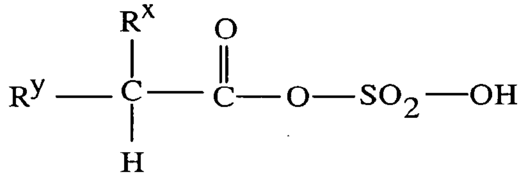
wherein R^1 and R^2 are each selected from the group consisting of alkyl, hydroxylalkyl radicals having 1 to 4 carbon atoms or in combination with the carbon atom to which they are attached they form a cycloalkyl group having 3 to 8 carbon atoms, and R^3 is selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbon atoms, and mixtures thereof, and R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are the same or different and are selected from the group consisting of hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons provided that at least one of R^4 or R^5 bonded to the carbon atom directly bonded to the nitrogen atom is an alkyl or hydroxyalkyl radical when R^3 is hydrogen, the process involving reacting a ketene of the formula



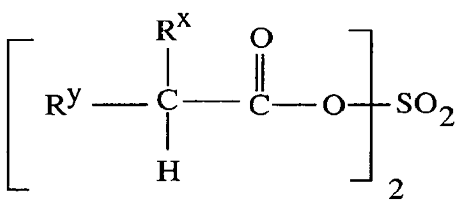
2c

wherein R^x and R^y are the same or different and are selected from the group consisting of hydrogen, alkyl radicals having 1-4 carbons, aryl radicals, aryl radicals bearing substituents selected from the group consisting of hydrogen and

one or more alkyl radicals having 1 to 10 carbons, and mixtures thereof, or R^x and R^y in combination with the carbon to which they are attached form a cycloalkyl radical having 3 to 8 carbons, with sulfuric acid to yield monoacylsulfate (3) and/or diacylsulfate (4) of the formula

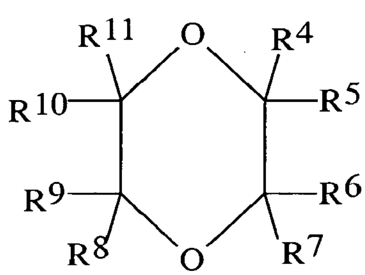


3c



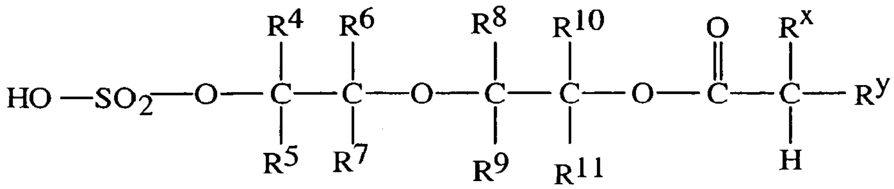
4a

which is then reacted with a dioxane of the formula

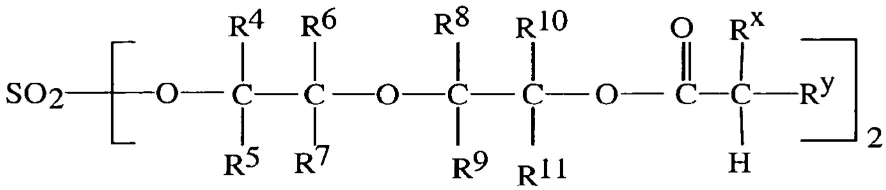


5

wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are the same or different and are selected from hydrogen, alkyl and hydroxyalkyl radicals having 1 to 4 carbons to yield products of the structure **6** and/or **7**:

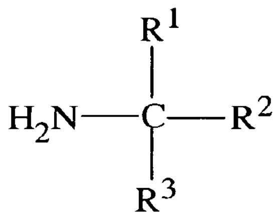


6c



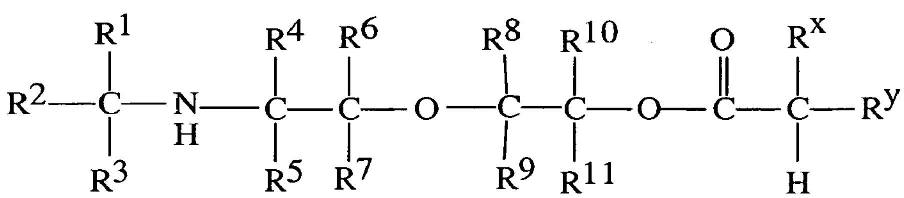
7a

and mixtures thereof, which are then aminated with an alkyl amine of the formula



8

wherein R^1, R^2 and R^3 are as previously defined to yield material of the general formula **9**



9a

which is then hydrolyzed with base to yield product (1).

17. The method of claim 16 wherein R^1, R^2, and R^3 are methyl radicals.

18. The method of claim 16 wherein R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are hydrogen, and R^x and R^y are hydrogen or phenyl.

19. The method of claim 16 wherein the base is selected from alkali metal hydroxide, alkali metal alkoxide, or alkali metal carbonate.

20. The method of claim 16 wherein R^1, R^2, and R^3 are methyl, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are hydrogen, and R^x and R^y are hydrogen or phenyl.

21. The method of claim 1, 6, 11 or 16 wherein the ketene, organic carboxylic acid halide, organic carboxylic acid anhydride, mixture of any two or of all three thereof, and the H_2SO_4 are reacted in about a stiochiometric ratio at a temperature between about -80°C to about 150°C, the resulting sulfate is reacted with the dioxane at a dioxane to sulfate ratio of about stoichiometric to about 10:1 to cleave the dioxane at a temperature between about -80°C to about 200°C, the resulting cleavage product is reacted with the alkyl amine in an amine to cleavage product mole ratio of about stoichiometric to about 10:1 at a pressure of from about atmospheric (1 bar) to about 100 bars, at a temperature of between about 40°C to about 200°C, and the aminated product is hydrolyzed with base at between about 20°C to about 110°C.

22. The method of claim 1, 6, 11 or 16 wherein the mixing of the ketene, organic carboxylic acid halide, organic carboxylic acid anhydride, mixture of any two or of al three, the sulfuric acid and the dioxane are combined in a single step, the reaction mixture being heated at a temperature of between about -80°C to about 200°C to produce a cleavage product, the cleavage product and the alkylamine are reacted at an amine to cleavage product ratio ranging from about stoichiometric to about 10:1 at a pressure from about atmospheric (1 bar) to about 100 bars at a temperature of between about 40°C to about 200°C, and the aminated product is hydrolyzed with base at between about 20°C to about 110°C.

SYNTHESIS OF SEVERELY STERICALLY HINDERED SECONDARY AMINOETHER ALCOHOLS FROM A KETENE AND/OR CARBOXYLIC ACID HALIDE AND/OR CARBOXYLIC ACID ANHYDRIDE

Abstract of the Disclosure

Severely sterically hindered secondary aminoether alcohols are prepared by a process comprising reacting a ketene with sulfuric acid to produce an anhydride which is then reacted with, to cleave the ring of, a dioxane to yield a cleavage product which is then aminated using an amine, followed by hydrolysis with a base to yield the desired severely sterically hindered secondary amineoether alcohol.